MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

OCTOBER 18, 1973

(A. T. N.)

# ACUTE TUBULAR NECROSIS

## ETIOLOGY AND MANAGEMENT

INDEX

INTRODUCTION:

Acute tubular necrosis, or A.T.N., is the most common problem seen in renal consultation. The diagnosis is frequently made on the basis of no prior history of a proven insult but merely on the basis of the circumstances and clinical course; e.g., a patient post operatively with decreasing urine output and a rising BUN unresponsive to fluids. The diagnosis is usually confirmed, not by biopsy, but by first, the fact that the patient recovers; and secondly, the manner of that recovery.

DEFINITIONS:

OLIGURIA - Less than 500 cc output in a 24 hour period. Roughly, the minimum volume of urine required to clear the patient's osmotic load.

ANURIA - Less than 100 ml urine output per 24 hours.

URINARY SODIUM - A spot specimen in A.T.N, usually has a concentration of between 40-90 mEq/L. A fair guide but early can be deceptively low.

"PRE RENAL" AZOTEMIA - Usually related to a decreased circulatory volume with poor renal perfusion and a decreased GFR. Urine sodium usually <20 mEq/L - responds to salt or expanders.

"POST RENAL" AZOTEMIA - Obstruction from any cause. Usual hallmarks are sudden decrease or increase in urine output. Sometimes varying outputs from day to day with stable intake and no losses suggest diagnosis.

A.T.N. -

1. Development of anuria over the course of a few days.
2. A low ratio of urine:plasma urea. U/P <5.
3. An endogenous creatinine clearance of <5 ml/min.
4. A TYPICAL HISTORY with a recognized condition of shock or other precipitating factors and/or A TYPICAL CLINICAL COURSE WITH RETURN OF RENAL FUNCTION.
5. Characteristic histological changes in renal tissue obtained by kidney biopsy and/or from a specimen of renal tissue RAPIDLY fixed post mortem.

"HIGH OUTPUT" RENAL FAILURE - A.T.N. where the anuric or oliguric phase lasted minutes or hours and patient is seen in the polyuric phase with a high or rising BUN/Cr.

SNGFR - Single nephron glomerular filtration rate as measured in the surface cortical nephrons usually of the rat.

p.c.t. - proximal convoluted tubule.

d.c.t. - distal convoluted tubule.

CLINICAL COURSE:

DEVELOPMENT:

The rapid (hours) or gradual (days) fall off in urine volume associated with a rise in BUN/Cr in spite of volume replacement and with no evidence of obstruction.

The history at this point often is the most important area; e.g., was cleaning upholstery with carbon tetrachloride.

BEWARE of partial response to volume in developing A.T.N.; e.g., output increases with 1 liter of saline but only 400 cc of 1000 cc given is put out.

ANURIC PHASE:

Very variable time course but upper limit is now 100 days (46) and with better care such as dialysis, it may be even longer. There is often 2 phases in this period depending on etiology. Hamburger (49) has shown nicely that catabolism is high initially and then levels off. Treatment must take this into account.

DIURETIC PHASE:

EARLY - When this finally occurs, urine output usually begins to double on succeeding days until a volume of 2-3 liters is reached.

BEWARE - During this period and even with outputs of 2 and 3 liters $K^+$ and BUN/Cr may still rise.

Bloomer (46) has cases where 11 and 17 days were required before patient could lower values on his own without dialysis.

REMEMBER - Dialysis with volume reduction and removal of osmotic load may blunt classic diuretic phase.

LATE - Once GFR is improving (>5 ml/min) output may remain high for months because of decreased ability to concentrate urine. (Sometimes introgenic because patients told "to drink lots of water".)

Merril (47) has correctly pointed out that massive salt loosing to the point of collapse is rare in this period.

RECOVERY:

AGE - In patients below 30 years of age, recovery is usually complete. Generally renal function has returned to normal by 3 months to 1 year if it is going to recover completely. As you go beyond age 30, there is a slow drop off as shown in the following table.

Effect Of Age At The Time Of
Acute Renal Failure On Subsequent Recovery

| Age | 2-20 | 21-40 | 41-60 | 61-80 |
|---|---|---|---|---|
| Number | 4 | 15 | 10 | 8 |
| $C_{Inulin}$ | 124 | 99 | 77 | 54 |

PREVIOUS DISEASE - The question of previous disease and recovery is less clear, being somewhat masked by the age factor. Most authors felt underlying disease did not hinder extent of recovery but did influence the rate.

PROGRESSION - In most series there were one or two patients who recovered and then began to loose function. This can most likely be explained by the patient having underlying disease that progresses since in most cases biopsies were not done.

CONCENTRATING ABILITY - While this is the last function to return, it does so to almost normal in most patients by 1 year.

1. Lewer, D.T., Mathew, T.H., Maher, J.F. and Schreiner, G.E. Long term follow-up of renal function and histology after A.T.N. Ann. Int. Med. 73:523, 1970.

*Best study of return of function long term.*

2. Balsløv, J.T. and Jørgensen, H.E. A survey of 499 patients with acute anuric renal insufficiency. Am. J. Med. 34:753, 1963.

*A large complete series before and after dialysis became available.*

3. Hall, J.W., Johnson, W.J., Maher, F.T. and Hunt, J.C. Immediate and long term prognosis in acute renal failure. Ann. Int. Med. 73:515, 1970.

*A good review of course and rate of recovery particularly as related to age.*

4. Kumar, R., Hill, C.M. and McGeown, M.G. Acute renal failure in the elderly. Lancet 1:90, 1973 (Jan. 13).

*A review of mortality and aging showing no difference in mortality when compared with a younger group.*

MORTALITY BEFORE AND AFTER 1960 COMPARED:

In 1960 Dr. Paul Teschan put forward the following hypothesis:

HYPOTHESIS
For Patients With Acute Renal Failure

1. The uremic syndrome is often largely reversible by dialysis procedures.
2. Uremic patients frequently develope sepsis and other complications which are not reversible by dialysis and commonly cause death.
3. These complications may reflect a cummulative injury of many tissues by the same toxic dialyzable substances that presumably produce the uremic syndrome.
4. THEREFORE, prophylatic dialysis applied before uremic symptoms appear should prevent both the uremic syndrome and many of its commonly lethal sequelae.

5. Teschan, P.E. et al. Prophylatic hemodialysis in the treatment of acute renal failure. Surgical Research 53:992, 1960.

*One of the few reports to prove the above hypothesis - used first 15 patients referred in?*

While Teschan's initial selected group seems to support his hypothesis, subsequent studies, shown in the table on the following page, do not support it at least by mortality figures.

MORTALITY RATES 1947-1972

| Author | Year | # Patients | % Mortality |
|---|---|---|---|
| Swann & Merril | 1953 | 85 | 44 |
| Alwall | 1954 | 62 | 31 |
| Anthonisen et al. | 1956 | 35 | 68 |
| Palmer & Henry | 1956 | 54 | 50 |
| Study Group of ARF | 1957 | 1044 | 49 |
| Bluemle et al. | 1959 | 100 | 50 |
| | HYPOTHESIS (1960) | | |
| Balsløv et al. | 1962 | 305 | 51 |
| Luding et al | 1964 | 178 | 58 |
| Kirkland et al. | 1965 | 400 | 58 |
| Kleinknocht | 1970 | 500 | 34 |
| Hall & Hunt | 1970 | 186 | 53 |
| Stott et al. | 1972 | 109 | 57 |
| Lordon & Burton | 1972 | 67 | 63 |
| Belfast Series | 1973 | 122 | 57 |

REASONS HYPOTHESIS SEEMS TO BE INCORRECT

KOREAN WAR vs VIET NAM WAR

Incidences of A.R.F. - Viet Nam vs Korea

| | K.W. | V.N. |
|---|---|---|
| Incidence/Hospitalized Patient | 1/200 | 1/6-700 |
| Weapons | ↓ Velocity Less Trauma | ↑ Velocity More Trauma |
| Evacuation Time | 6.3 hrs. | 2.8 hrs. |
| Osmotic Agents | No | Yes |

CHANGING PATIENTS & COURSE OF TREATMENT:

1. Patients are now kept alive for more than a few days by controlling major complications; e.g., K and uremia.

2. Infections in the past were disregarded as a terminal event.

3. Patient population is changing. We now treat patients we would never have tried to save in the past.

4. Increase in maneuvers to support life have complications; e.g., indwelling catheters.

CAUSES OF DEATH:

In early series the causes of death were hyperkalemia, pulmonary edema and GI hemorrhage. Now dialysis has allowed control of potassium and fluids and the incidence of hemorrhage has been decreased. But infection has now become the major cause of death.

If we look at Lordon's causes of death in his young men we see the following figures supporting this change.

CAUSE OF DEATH IN FORTY-TWO PATIENTS

| Diagnosis | No. of Patients | % of Total |
|---|---|---|
| Gram-negative sepsis | 31 | 72 |
| Hemorrhage | 4 | 10 |
| Pulmonary edema | 2 | 5 |
| Hyperkalemia | 2 | 5 |
| Miscellaneous | 3 | 8 |
| Brain damage | 1 | |
| Air embolism | 1 | |
| Undetermined | 1 | |

TYPES OF INFECTION:

Again using Lordon's results we see that while most are infected to some degree, certain types of infection are more serious. Similar findings were present in the Mayo and Belfast study of civilian populations.

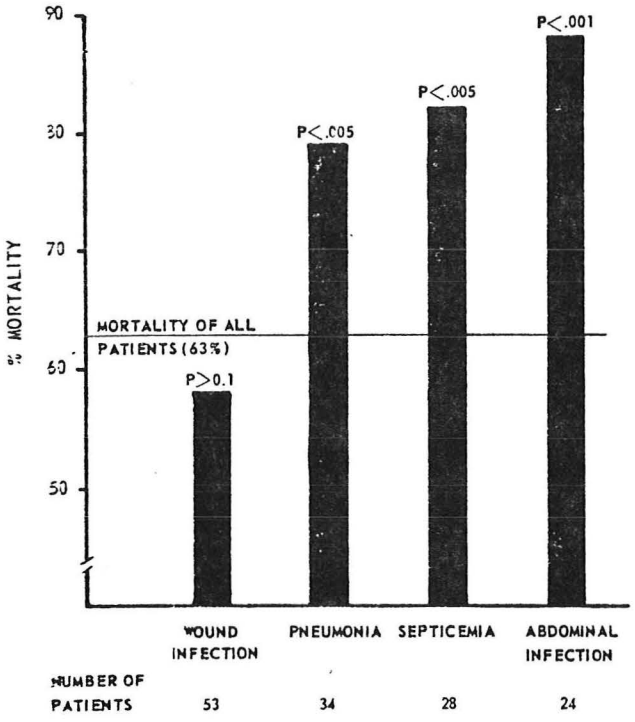



Fig. 1 (6)

MEDICAL vs SURGICAL A.T.N.:

In all series non surgical, non infected patients show a high degree of survival when compared to surgical. The classic example of medical A.T.N. would be CARBON TETRACHLORIDE. Mortality in this group should be almost zero. The incidence then rises in obstetrical type patients to a mortality of 10-25% depending on the series. In the surgical group of A.T.N., our experience here of 50%+ if surgery other than the abdomen and 80%+ mortality on abdominal wounds with A.T.N. is supported in most studies. (4,8)

WE MUST BE AWARE THAT INFECTIONS ARE THE MAJOR COMPLICATION AT PRESENT AND DO EVERYTHING WE CAN TO PREVENT THEM.

6. Lordon, R.E. and Burton, J.R. Post traumatic renal failure in military personnel in Southweast Asia. Am. J. Med. 53:137, 1972.

*An excellent review of the changes in war casualties over the years. The problems of infection are well shown.*

7. Montgomerie, T.Z., Kalmanzon, G.M. and Guzle, L.B. Renal failure and infection. Medicine 47:1, 1968.

*A detailed review of infective complications and causes in a V.A. population.*

8. Stott, R.B., Ogg, C.S., Cameron, J.S. and Berwick, M. Why the persistent high mortality in acute renal failure. Lancet 2:75, 1972 (July 8).

*A good review of mortality and its relationship to infection with an excellent discussion as to why such patients still die.*

PATHOLOGICAL FINDINGS:

In NO other entity in renal disease is the pathology of so little help. In most series, at present, biopsies are not done unless the recovery course is atypical or some other lesion is suspected.

GROSS:

Swollen kidneys with definite increase in size.

The cut surface bulges out.

Acutely cortex is pale and wide.

Acutely medulla is dark and congested.

MICROSCOPIC:

GLOMERULI -

No significant lesion by lite or EM.

May be congested early but later appear bloodless

Protein may appear in Bowman's space and the cells lining Bowman's capsule may become prominent. (TUBULIZATION)

TUBULES -

Proximal Tubule - Varies with time course.

Unequivocal necrosis is RARE.

Post mortem findings are identical.

Spotty lesions with flattened epithelium and ↑ Basophilia with dark stained nuclei.

Fine vacuolization with sugars or mannitol.

Henle's Loop - Casts may be present.

Necrosis variable but more common in toxic models in rats; e.g., Oliver's studies (10).

Distal Tubule - Necrosis rare (5/33).

Flattening and dilatation common (27/33).

Collecting - Casts often present.

Polys may be present.

Interstitial Tissue - Generalized edema, particularly in boundary zone. Polys may be present.

Blood Vessels - Micro thrombi may be seen; become more significant in cortical necrosis.

Electron Microscopy - Mitochrondrial changes in tubules.

Loss of brush border in p.c.t.

REMEMBER: In some models, absolutely zero correlation with function.

9. Heptinstall. Pathology of Kidney. Boston, Little Brown, 1966.

*An excellent section on both A.T.N. and A.C.N. with all pertinent references.*

10. Oliver, J., MacDowell, M. and Tracy, A. The pathogenesis of acute renal failure assoicated with traumatic and toxic injury. J. Clin. Invest. 30:1307, 1951.

*The support article for 2 basic lesions.*

1. *Nephrotoxic - ? necrosis but intact basement membrane in p.c.t.*
2. *Tubulorhexis - anywhere, but particularly distally with disruption of basement membrane (this is probably secondary to ischemia).*

*The major problems are the fact that only a moderate % of the nephrons are involved. Functional correlations are without clinical support.*

11. Price, J.D.E. and Palmer, R.A. A functional and morphological follow up of acute renal failure. Arch. Int. Med. 105:90, 1960.

*Only study with persistent glomerular and tubular lesions. Seem to be overreading non specific and artifactual findings.*

URINALYSIS:

May show anything and everything.

Proteinuria - common but not usually massive.

RBC - usual

WBC - common

Bacteria - often later

Casts - variable, sometimes increase with diuretic phase

Sugar - can be present

Urine Sodium - helpful but may be low (below 30 mEq/L) early

Urea - urine to plasma ratio, <5, usually only supporting evidence

Osmolality - approaches plasma

Myoglobin - should be checked

PATHOPHYSIOLOGY:

At the present time there are 3 major theories.

PATHOGENESIS OF ACUTE TUBULAR NECROSIS

1. Obstruction of Tubular Lumen
   A. Intrinsic - cast formation; cellular debris or pigment
   B. Extrinsic - interstitial edema
2. Tubular Leakage
3. Vasospastic - A marked reduction in blood flow with a decrease in glomerular filtration rate per nephron (SNGFR)

12. Flamenbaum, W. Pathophysiology of acute renal failure. Arch. Int. Med. 131:911, 1973.

*The best review available on studies to elucidate the mechanisms of A.T.N. (Excellent)*

OBSTRUCTION:

If this were the mechanism one would expect an INCREASE IN INTRATUBULAR PRESSURE. Flannigan and Oken (13), using the $HgCl_2$ model of acute renal failure in rats did micropuncture on proximal tubules. In their studies early changes (4-8 hours) showed a decrease in pressure from control animals. At 8-26 hours pressure continued to be decreased. All pressures obtained were well below the estimated intraglomerular pressure. In addition, such studies (14) showed that casts when present in the pigment models (glycerol), moved very easily at pressures well below filtration pressure. Interstitial edema is likewise untenable in the face of low intratubular pressure.

In addition to these studies and others that support them pathological findings do not show obstruction. For what they are worth, microscopy shows casts are not a major finding in most acute tubular studies. Also, there is no evidence for widely dilated proximal tubules which should be present with significant distal obstruction.

If intratubular obstruction has any role, it is merely as a slight adjunct after the main event has occurred.

13. Flannigan, W.J. and Oken, D.E. Renal micropuncture study of the development of anuria in the rat with mercury-induced acute renal failure. J. Clin. Invest. 44:449, 1965.

*Techniques used for micropuncture are described with pressure changes.*

14. Oken, D.E., Arce, M. and Wilson, D.R. Glycerol induced hemoglobinuric acute renal failure in the rat. I. Micropuncture study of the development of oliguria. J. Clin. Invest. 45:721, 1966.

*Plays down cast formation as a possible etiological mechanism.*

15. Meroney, W.H., Rubini, M.E. Kidney function during acute tubular necrosis. Clinical studies and a theory. Metabolism 8:1, 1959.

*Clinical study of ten patients. Thinks any urine out is from undamaged tubules. Damaged tubules are blocked by debris. No data, but presents a theory.*

16. Peters, J.T. Oliguria and anuria due to increased intrarenal pressure. Ann. Int. Med. 23:231, 1945.

*Suggests decapsulation to decrease intrarenal pressure. Treatment might be worse than disease.*

TUBULAR LEAKAGE:

Passive backflow has been a popular theory ever since Richard's (17) direct observation with dye injection that the kidney turned red but little came out in the urine. The GFR remained normal in these studies after mercuric chloride administration with a brisk proximal tubule flow but the rats became anuric. Further support for this theory comes from Bank's (18) work, again using mercuric chloride as the inducing agent but with lyssamine green as the dye. In his studies the dye was seen in the proximal tubules but did not appear distally as it did in the control animals. Bank found a 63% drop in SNGFR as measured late vs early in proximal tubule and there was a further decrease in the value in distal tubules. Another supporting study was that of Sternhausen (19) who injected $^{14}C$-labeled inulin into the proximal tubule and found it appeared unlike controls in the other kidney in mercury chloride treated rats. He interpreted this as showing that inulin, a non reabsorbable substance, leaked from the tubule and got back into the blood stream and was excreted in the other kidney. In summary, this theory would hold:

1. Normal GFR early in p.c.t.
2. A decreasing GFR as one progresses down the tubule.
3. Leakage of material out as it progresses down the tubule.

However, many other workers have not been able to reproduce Bank's findings or support this hypothesis with further studies. Oken's (12) group showed a fall in SNGFR early in the p.c.t. Barenberg and his co-workers (20) found that not only was overall GFR decreased, but SNGFR was down equally in the early p.c.t. and remained down throughout the nephron.

If we assume a leak is present, then variable size molecules should leak at a different rate and hence have different clearances because of the altered permeability and leak rate. Dibona (21), in Oken's group used mannitol (5500 mol. wt.) and inulin (180 mol. wt.) and did clearance studies. Both substances were depressed equally, again raising questions about the back leak theory. Uranyl nitrate studies (12) further showed little tubular damage histologically early (6 hours) yet inulin clearance was 1/4 of normal.

Subsequent studies in all models have not supported the back leak view. In fact, evidence from these studies showing that SNGFR was decreased immediately in the early p.c.t. lead to the subsequent ressurection of some neglected work by Goormaghtigh in the 1930 & 40's (22).

17. Richards, A.N. Direct observations of change in function of the renal tubule caused by certain poisons. Trans. Am. Assoc. Phys. 44:64, 1929.

*A true direct observation that still has not been completely explained. The micropuncture part of the study may be less secure.*

18. Bank, N., Mertz, B.F. and Aynedjian, H.S. The role of "leakage" of tubular fluid in anuria due to mercury poisoning. J. Clin. Invest. 46:695, 1967.

*A good paper, unfortunately the studies have not been verified.*

19. Steinhausen, M. - in German; quoted in reference #12. Pflugers Arch. 277:23, 1963.

20. Barenberg et al. Clearance and micropuncture study of renal function in mercury chloride treated rats. J. Lab. Clin. Med. 72:473, 1968.

*A good study that takes into account the time the lesion has been present and discusses the role this might play.*

21. Dibona, G.F., McDonald, F.D., Flamenbaum, W., Dammin, G.J. and Oken, D.E. Maintenance of renal function in salt loaded rats despite severe tubular necrosis induced by $HgCl_2$. Nephron 8:205, 1971.

*An excellent paper showing not only that there is little evidence for back leak but that saline can protect the rat from clinical A.T.N.*

22. Goormaghtigh, N. Vascular and circulatory changes in renal cortex in the anuric crush-syndrome. Proc. Soc. Exp. Biol. Med. 59:303, 1945.

*A short classic paper where the author for once in English gives very briefly his views regarding A.T.N., eclampsia and acute malignant glomerular nephritis.*

VASOSPASTIC:

All this work to disprove the first two theories began to bring forward some new evidence to support older work. It was evident that in most studies GFR decreased early (12,20). Additional work was carried out on the uranyl nitrate model using radioactive Xenon and trying to correlate it with renal blood flow (12). These investigators showed that while there was an overall decrease in renal blood flow there was a more marked decrease in the outer cortical flow. This redistribution has now been supported clinically by Hollenberg (23) and in other rat models (24) along with reversal of the phenomena with recovery of kidney function.

A number of workers initially from Oken's group and later individually, plus other investigators, have shown the following points to hold true with A.T.N. in many models.

1. Overall GFR decreases (25), the extent depends on the inducing substance and the animal model.

2. Superficial SNGFR decreases promptly in all models (13,20).

3. Renal blood flow falls but outer cortical flow falls more and correlates with recovery of function in many cases (25).

4. Plasma renin values are elevated in all models of A.T.N. particularly early (27-29).

5. Renin depleted animals go through the same course but A.T.N. is not produced although tubular damage does develop (12,25,26).

23. Hollenberg, N.K. et al. Acute renal failure due to nephrotoxins, renal hemodynamics and angiographic studies in man. New Eng. J. Med. 282:1329, 1970.

*A good review of the correlation of the angiogram to washout studies. He probably pushes washout too hard.*

24. Chedru, J.F., Baelhke, R. and Oken, D.E. Renal cortical blood flow and glomerular filtration in myohemoglobinuric acute renal failure. Kidney Int. 1:232, 1972.

*Good correlation of renal and cortical blood flow with onset and recovery from acute glycerol induced renal failure.*

25. McDonald, F.D., Thiel, G., Wilson, D.R., Dibona, G.F. and Oken, D.E. The prevention of acute renal failure in the rat by long term saline loading. A possible role of the renin-angiotensin axis. Proc. Soc. Exp. Biol. Med. 131:610, 1969.

*A good basic paper on the possible role of salt and renin depletion as protection from A.T.N.*

26. Theil, G., McDonald, F.D. and Oken, D.E. Micropuncture studies of the basis for protection of renin depleted rats from glycerol induced acute renal failure. Nephron 7:67, 1970.

*Further studies from the same group.*

27. Tu, W.H. Plasma renin activity in acute tubular necrosis and other renal diseases associated with hypertension. Circulation 31:685, 1965.

*An attempt to show the renin mechanism in action for different types of renal disease.*

28. Brown, J.J. et al. Renin and acute renal failure: Studies in man. Brit. Med. J. 1:253, 1970 (Jan. 31).

*An early attempt to relate renin values to acute tubular necrosis testing Goormoghtigh's original hypothesis.*

29. Ochoa, E., Finkielman, S. and Agrest, A. Angiotensin blood levels during the evaluation of acute renal failure. Clin. Sci. 38:225, 1970.

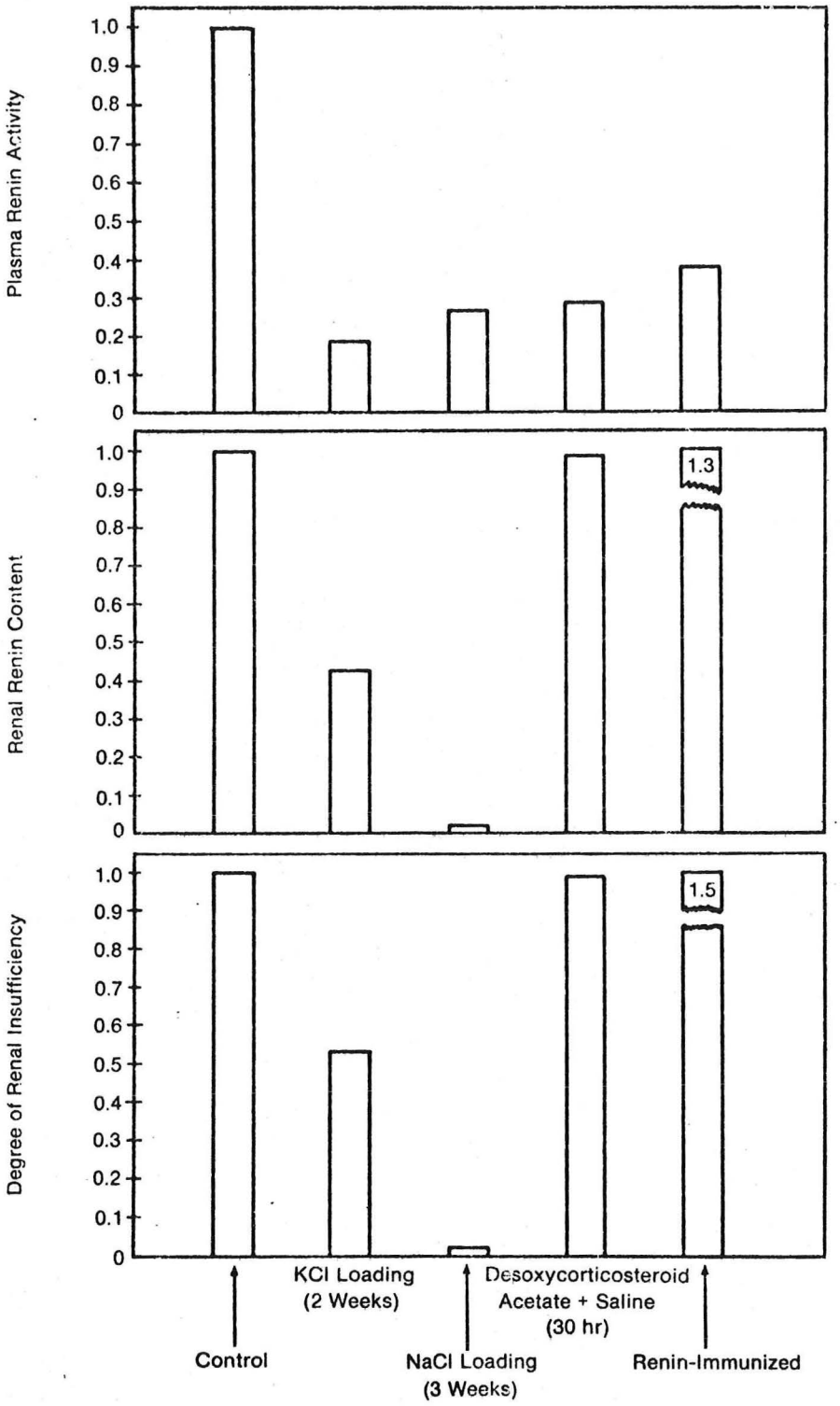
*Further studies in an attempt to correlate renin and renal failure.*

30. Thurau, K., Schnermann, J., Nagel, W., Horster, M. and Wahl, M. Coroposition of tubular fluid in the macula densa segment as a factor regulating the function of the juxtaglomerular apparatus. Circ. Res. Supp. Vol. 20 & 21, pp 11-79, July 1967.

*Early work showing sodium concentration at macula densa may influence GFR in that nephron. Good discussion following paper.*

31. Thurau, K.W.C. et al. Activation of renin in single juxtaglomerular apparatus by sodium chloride in the tubular fluid at the macula densa. Circ. Res. Supp. Vol. 30 & 31, September 1972.

*Continuation of above study, perfusion with different fluids and actual measurements of renin at juxtaglomerular apparatus.*




Comparison of plasma renin activity (PRA), renal renin content (RRC), and course of acute renal failure (extent of azotemia) in various experiment groups.

Fig. 2 (12)

Problems With The Vasospastic Model:

1. Renin is not permanently elevated in all models during anuria (33).

2. Not all models behave exactly the same with regard to anuria (12).

3. Obstruction may also play some part in feed back to decrease GFR (32).

4. Elevated renin could be due to something else and not causally related to decreasing renal blood flow (28).

5. Sympathetic nerves could produce this same response (34) (however, it can occur in the denervated transplant kidney).

In Favor of Vasospastic Model:

1. Renin content is greatest where ischemia occurs - the outer cortex (5).

2. Angiotensin I can be converted to angiotensin II in the cortical area (36).

3. Renal lymph contains high concentration of renin and angiotensin (higher than the blood).

32. Flamenbaum, W., McDonald, F.D., Dibona, G.F. and Oken, D.E. Micropuncture study of renal tubular factors in low dose mercury poisoning. Nephron 8:221, 1971.

*Suggests a secondary feed back to glomerulus by a pressure mechanism if tubule is blocked distally.*

33. Hayes, J.M., et al. Renal renin and renin release in acute renal failure in the rat. (Abstract) Fed. Proc. 27:629, 1968.

*Values show renin levels decrease after control period.*

34. Wagermark, J., et al. Sympathetic inervation of the juxtaglomerular cells of the kidney. Circ. Res. 22:149, 1968.

*Support for alternate theory for vasoconstriction.*

35. Brown, J.J. et al. Assay of renin in single glomeruli: Renin distribution in the normal rabbit kidney. Lancet 2:668, 1968.

*Support for localization theory of renin and its relationship to function intrarenally.*

36. Granger, P., Dahlheim, H. and Thurau, K. Enzyme activities of the single juxtaglomerular apparatus in the rat kidney. Kidney Int. 1: 78, 1972.

*Suggests converting enzyme present to allow angiotensin II to act directly on vasculature in glomerulus.*

ACUTE CORTICAL NECROSIS: (A.C.N.)

Differs from A.T.N. in that the whole cortex becomes necrotic and dies. This is an extreme form and focal or patchy cortical necrosis has been reported with acute tubular necrosis in some of the intervening areas (37). Moore and Sheehan have produced the definitive study and they suggest the following course. (38)

1. Initial Ischemic Period (4-6 hrs) - this produces death of tubular and glomerular cells in the cortex.

2. Return of blood flow through the ischemic area (8-12 hrs). Fibrin thrombi are formed at this time.

3. Second period of ischemia "operative spasm" of intratubular arteries (6-8 hrs or longer).

4. Brief second period of return of flow - dilatation of glomeruli and arterioles with thrombi formation in the now dead tissue.

The entity is seen most commonly in severe acute pancreatitis, septicemia and particularly after obstetrical catastrophies; e.g., abruptio In this center we have not seen a case that was treated in Parkland Hospital. I believe the reason is the rapid use of fluids and blood by our Ob/Gyn department that shortens the initial ischemic period and aborts some irreversible cases of A.C.N. to reversible A.T.N.

37. Renal failure in blunt trauma. Clinicopathologic conference. Washington Univ. School of Medicine. Am. J. Med. 50:368, 1971.

*Evidence for mixture of A.T.N. and A.C.N. - good discussion by Dr. Saulo Klahr.*

38. Sheehan, H.L. and Moore, H.C. Renal cortical necrosis and the kidney of concealed accidental hemorrhage. Springfield Ill. Thomas, 1953.

*Definitive work on the subject.*

TREATMENT:

PREVENTION:

Like most diseases, prevention would be the best cure. The investigative studies presented in the previous section all suggest that salt loading (by what every mechanism) blunts the course or prevents A.T.N. Therefore, it would seem mandatory that we prepare patients before they face a known possible A.T.N. producing injury. The renal service has had one consult in the last year pre op where this approach was used.

SUGGEST:

1. SALINE + small amount of LASIX
2. SALINE + mannitol

NOTE: must give volume

ACUTE INTRAVENTION:

No one is certain when it is "too late" after the insult to try and abort it. Therefore, a combination of the following should be used.

1. Volume - must always be first.
2. Mannitol - a trial 12 1/2 gms once, I.V. over 5 min; if NO response after 2 doses STOP.
3. Diuretics - Lasix. 100 mgm I.V., push once. Above this (?) but not more than 200 mgm.
4. Expanders - Whole blood, albumin. Dextran, only as a last resort.

39. Luke, R.G., Buggs, J.D., Allison, M.E.M. and Kennedy, A.C. Factors determining response to Mannitol in acute renal failure. Am. J. Mec. Sci. 259:168, 1970.

*An article that tires to come to grips with this difficult problem in its clinical setting. Suggests if urine:plasma osmolality ratio is >1.05 and duration of insult <50 hrs, 20-60 gms of mannitol should be tried and a response would be predicted.*

40. Silverberg, D.S., Johnson, W.J. The use of mannitol in oliguric renal failure. Med. Clin. of N.A. 50:1159, July 1966.

*A detailed paper on uses and side effects.*

41. Cantarvich, F., Fernandez, J.C., Locatelli, A. and Perez, Loredo, J. Furosemide in high doses in the treatment of acute renal failure. Postgraduate Med. J. April Supp. 13, 1971.

*Suggests that if enough furosemide is given, anything will urinate. One of rare papers that suggest GFR and function is improved with the diuretic.*

42. Postgraduate Med. J. April Supp., 1971.

*A series on furosemide in renal failure. Very biased in favor of the drug. Good baseline review but must be considered skeptically.*

43. Kjellstrand, C.M. Ethacrynic acid in acute tubular necrosis. Indications and effect on the natural course. Nephron 9:337, 1972.

*Effective if used before 22 hours. States that it alters course of A.T.N. (?). 2 became deaf of 11 treated; 1 permanently.*

If NO response or a limited decreasing response then *STOP FORCING FLUIDS*. Many of the problems in the developing stage of A.T.N. are caused by forcing fluids.

The use of progressively increasing amounts of Lasix (40,41) is questionable and the side effects; e.g., hearing loss are great (42).

DECIDE: ONCE AN ADEQUATE TRIAL HAS BEEN GIVEN, STOP AND THEN BEGIN CHRONIC CONSERVATIVE MANAGEMENT.

CHRONIC MANAGEMENT:

1. Fluids - insensible (300-500 cc/24 hrs for 70 kg man) plus output. Remember to replace G.I. losses.

2. Diet - whatever patient will take. At least 100 gms carbohydrate/day for protein sparing. (I.V. if necessary as 10 or 50% glucose) Particularly high biological value (H.B.V.) protein.

Measurements of Catabolism in Battle Casualties with Renal Failure Compared to that Estimated for an Anuric Patient with Normal Metabolism

| | Mean Daily Rise in Azotemia (mg%) | Mean Daily Rise in Potassium (mEq/L) | Mean Daily Weight Loss (kg) |
|---|---|---|---|
| Korean conflict | 50 (NPN) | 0.7 | 1.0 |
| Vietnam conflict | 32 (BUN) | 0.95 | 0.9 |
| Normal (estimated)* | 12 (NPN)<br>8 (BUN) | 0.32 | 0.25-0.5 |

NOTE: NPN - nonprotein nitrogen; BUN - blood urea nitrogen.

*From Strauss (47) and Maher et al. (1).

3. Electrolytes -

a. Hypocalcemia - only treat hypocalcemia if positive Trusseau sign present. Treatment is rarely if ever necessary.

b. Hyperuricemia - may be very high early but obstruction rarely seems to be a problem; usually not necessary to treat.

c. Hyperphosphatemia - treat with antacids, also protects G.I. tract; nausea with these agents is a major problem.

d. Potassium - hypokalemia is rarely if ever a problem.

Hyperkalemia should be treated as follows:

1. Alkalinization - sodium bicarbonate I.V., push 1 amp (44 mEq) and then as indicated by EKG.

2. Resins - Sodium exchange given by mouth with sorbital or as enema.

3. Calcium I.V. - to raise serum level

4. Glucose & Insulin - if nothing else

5. Dialysis - no place in acute treatment. May be necessary in chronic management.

6. Find Cause - tissue breakdown; pH shift; exogenous intake.

4. Dialysis -

When to dialyze is a major question. The following are some "rules of thumb" to use as a guide.

a. NEVER, unless you are forced to

b. Creatinine rise must be <u>balanced</u> against increasing urine volume if present. If a creatinine peak at 12 mg% or less, can be achieved; usually NO need to dialyze.

c. Hyperkalemia due to tissue breakdown

d. Fluid overload

e. Wound healing ?

f. If must dialyze, then do it early. Serum creatinine 6-8 mg%. Don't wait for conservative measures to fail.

Peritoneal Dialysis vs Hemodialysis:

Peritoneal - if one dialysis is all that seems necessary

No previous abdominal surgery. Remember, P.D. catheter can be placed at surgery

No severe pulmonary embarrassment

Hypotensive patient

No facilities for hemodialysis

Hemodialysis - if long term dialysis required. Remember vessels must be sacrificed to do hemodialysis. Save one arm if you think dialysis may become chronic - for fistula placement.

5. "Hyperalimentation" -

In the absence of organized teams or someone directly responsible the risks are probably too high (45). When such support is available, it should be utilized. Probably all patients requiring dialysis and all post surgical renal failure patients with limited or absent oral intake should be supplemented. Abel and associates (44), in one of the few controlled studies on the subject showed a difference in 2 randomly selected groups of patients. The differences seem more significant when the major infectious complications were present; e.g., septicemia or pneumonia.

44. Abel, et al. Improved survival from acute renal failure after treatment with intravenous essential L-amino acids and glucose. New Eng. J. Med. 288:695, 1973.

*A controlled study of the use of amino acid and glucose supplementation in renal failure. Results appear to be very significant particularly in the more severely ill patients.*

45. Walker, C. Total parenteral nutrition. Med. Grand Rounds. PMH October 4, 1973.

*An excellent review of the total subject with a section on renal failure.*

6. Antibiotics - utilized as cultures indicate and not prophylactically.

LONG TERM RESULTS:

If the complications can be controlled, then most patients should recover (6,3). Renal function in A.T.N. always seems to recover enough to support life without dialysis (46). Some patients will be misdiagnosed and have acute cortical necrosis or some additional disease; e.g., undiagnosed multiple myeloma. One must be prepared to move these patients to chronic dialysis and/or transplantation.

The very recent literature (3,4,8,49) points out that we have neglected this acute recoverable form of renal disease and concentrated too much effort on chronic, non reversible and endlessly costly forms of renal disease. As Stott (8) maintains, once these patients recover, they require NO long term treatment.